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The role of diabetes mellitus in the aetiology of renal cell cancer

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Summary To investigate the relation between diabetes mellitus and the risk of renal cell cancer we carried out a population-based retrospective cohort study. Patients identified in the Swedish Inpatient Register who were discharged from hospitals with a diagnosis of diabetes mellitus between 1965 and 1983 formed a cohort of 153852 patients (80005 women and 73847 men). The cohort members were followed up to 1989 by record linkage to three nation-wide registries. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) were computed using age-specific sex-specific and period-specific incidence and mortality rates derived from the entire Swedish population. After exclusion of the first year of observation, a total of 267 incidences of renal cell cancer (ICD-7:180.0) occurred in diabetic patients compared with the 182.4 that had been expected. Increased risks were observed in both women (SIR = 1.7, 95% confidence interval, CI = 1.4–2.0) and men (SIR = 1.3; 95% CI = 1.1–1.6) throughout the duration of follow-up (1–25 years). A higher risk was seen for kidney cancer (ICD-7:180) mortality (SMR = 1.9; 95% CI = 1.7–2.2, women; SMR 1.7, 95% CI = 1.4–1.9, men). In comparison with the general population, patients with diabetes mellitus have an increased risk of renal cell cancer. [Diabetologia (1999) 42: 107–112]

Keywords Kidney neoplasms, diabetes mellitus, cohort study, risk factors, Sweden.

Malignant tumours of the kidney account for 2–3% of all new cancer patients in Sweden and several western countries, with incidence rates of 8–15 per 100000 person-years [1, 2]. Cancer of the renal parenchyma (renal cell cancer) accounts for 83% of the kidney cancer patients, renal pelvis cancer for 11%, and cancer at unspecified sub-sites for 6% [1]. Established risk factors for renal cell cancer, mainly cigarette smoking [3], obesity [4] and hypertension or use of antihypertensive medications [5], can explain only a small part of the occurrence of this malignancy.

Case-control studies of renal cell cancer that investigated the role of diabetes mellitus generally found no [6–8] or non-statistically significant [9, 10] excess risk, although an increased risk was seen in the largest study to date [11]. Some studies found an association confined to women [12–16]. Excess risks have also been reported in some cohort studies of patients with diabetes [17, 18], while others found no association [19–21]. Several autopsy studies have found a high prevalence of diabetes among kidney cancer patients [22–24]. Since the kidney is exposed for a long and sustained period to pro-insulin products with some homology to the insulin-like growth factor (IGF)-I prior to and during the course of diabetes mellitus [25], a role for diabetes in renal carcinogenesis appears plausible. To further examine this relation and to provide precise risk estimates, we

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Abbreviations: SIR, Standardized incidence ratio; SMR, standardized mortality ratio; CI, confidence interval; IGF, insulin-like growth factor; TGF, transforming growth factor; EGF, epidermal growth factor.

analysed the largest population-based cohort of diabetic patients studied so far, with essentially complete follow-up of up to 25 years.

Subjects and methods

The cohort. Because there is almost no private inpatient treatment in Sweden, hospital-provided medical services are, in effect, population-based and referable to the county in which the patient lives. Beginning in 1964/1965, the National Board of Health and Welfare started collecting data on individual hospital discharges in the Inpatient Register. Besides national registration numbers (unique personal identification assigned to all Swedish residents), each record contains data on the hospital department and up to eight discharge diagnoses, coded according to the seventh revision of the International Classification of Diseases (ICD-7) up to 1968 and according to the eighth revision thereafter. The number of hospitals delivering data to the register has increased steadily: in 1969, the register covered 60 % of the Swedish population, in 1978 this percentage was 75 %, reaching 85 % by the end of 1983. More detailed descriptions of this Inpatient register have been reported previously [26, 27].

All patients recorded in the Swedish Inpatient Register with a first discharge diagnosis of diabetes (ICD-7 code: 260, ICD-8 code: 250) between 1965 and 1983 were identified by use of the national registration number. A total of 216 827 unique national registration numbers were recorded in the register with at least one in-hospital episode and a diabetes diagnosis during this time period.

Follow-up. Record-linkage, based on the national registration number, to the nationwide Registry of Causes of Death led to information on the causes and date of death among those deceased up to 1989. A corresponding linkage to the Register of Population Migration identified dates of emigration. The national Swedish Cancer Registry, founded in 1958 and close to 98 % complete [28], was used to ascertain all incident cancers diagnosed in the cohort from the start of follow-up until the end of 1989. The Cancer Registry has had coded malignant diseases according to the ICD-7 classification during the entire period of study. Kidney cancer, ICD-7 code 180, is subdivided on the 4-digit level into renal parenchyma (180.0), renal pelvis (180.1), and part unspecified (180.9) [29]. The time of observation was from the date of entry into the cohort (date of first hospital discharge) until the first occurrence of any cancer, death, or the end of the observation period (31 December 1989), whichever came first.

To remove entries in the cohort with incorrect national registration numbers, which would otherwise contribute person-years of no risk, we also linked the cohort file to the Register of the Total Population. If a national registration number was incomplete or could not be found in any of the above-mentioned registers, that record was excluded. This led to exclusion of 25 415 (11.7 %) national registration numbers. Another 6606 (3.0 %) records were excluded due to date inconsistencies revealed during the record linkage and 14 881 (6.9 %) died during the index admission. Finally, we excluded 16 073 (9.4 %) patients because of prevalent cancers. Thus, a total of 153 852 patients were entered into the study. The mean ages at entry were 65.2 years for women and 60.5 years for men. Only 13 216 (8.6 %) of the cohort members were younger than 30 years of age at entry, of the remainder 7323 (4.8 %) were 30–39 years, 9153 (6.0 %) 40–49 years, 19 773 (12.8 %) 50–59 years and 104 387 (67.8 %) 60 years or older. The study cohort is further characterized in Table 1.

Table 1. Characteristics of patients assigned a hospital discharge diagnosis of diabetes mellitus in Sweden 1965–1983 with follow-up up to 1989

Characteristic	Women	Men
Number of patients	80,005	73,847
Total number of person-years	539,592	497,825
Average age at entry	65.2	60.5
Average years of follow-up	6.7	6.7
Average calendar year at entry	1977	1977
Number of renal cell cancers[a]	173	189
Average age at cancer diagnosis	74.6	72.5

[a] Of these cancers, 95 diagnosed during the first year of follow-up were excluded from all analyses

Statistical analysis. The standardized incidence (SIR) and mortality (SMR) ratios, defined as the ratio of observed number of cancers and deaths, respectively, to those expected, were used as measures of relative risk. The corresponding 95 % confidence intervals (CI) were calculated on the assumption that the observed number follows a Poisson distribution [30]. The expected numer of cancers was calculated by multiplying the number of observed person-years for each sex by age-specific cancer incidence rates for each 5-year age-group and calendar year of observation. These expected rates were derived from the entire Swedish population. In order to avoid ascertainment bias, cancers first diagnosed at autopsy were neither counted in the observed cases nor in the expected rates. We also calculated expected numbers of deaths using the same principles as in the incidence analyses. For the main analyses, we excluded the person-years that elapsed in the first year of follow-up, the kidney cancer cases that were detected and the deaths that occurred in the same period, to minimize the possible impact of selection bias. Such bias would occur if diabetes patients who fall ill or die from renal cell cancer within one year are more likely to be admitted to hospital than diabetes patients in general. Only first primary cancers were considered for the incidence analyses. In addition, analyses were made with multiplicative Poisson regression models including year of birth, year of follow-up, calendar time, age and sex in the same model, and the results did not importantly change compared with the stratified analysis. Furthermore, we included models with obesity and hypertension. As these analyses did not substantially change the estimates, we mainly present the stratified analyses.

Approvals from the Ethics Committee, Uppsala University and from the Swedish Data Inspection Board were obtained for the record linkages necessary for this study.

Results

A total of 362 incident renal cell cancers (ICD-7 : 180.0) occurred in men and women during the 1 037 417 person-years of observation. Person-years and kidney cancer incidences diagnosed during the first year of follow-up were excluded from further analyses, among them 95 renal cell cancer (ICD-7 : 180.0) (SIR = 3.0, 95 % CI = 2.4–3.7) and 10 renal pelvis cancer (ICD-7 : 180.1) patients (SIR = 2.6, 95 % CI = 1.2–4.7).

Table 2. Standardized incidence (SIR) ratios with 95 % confidence intervals (CI) for kidney cancer (ICD-7 : 180) during 1–25 years of follow-up among patients with diabetes mellitus

Cancer site	Outcome	Women				Men				Both sexes			
		Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI
Kidney[a]		161	94.5	1.7	1.5–2.0	176	130.4	1.4	1.2–1.6	337	224.9	1.5	1.3–1.7
Parenchyma (ICD-7 : 180.0)		126	75.8	1.7	1.4–2.0	141	106.6	1.3	1.1–1.6	267	182.4	1.5	1.3–1.7
Pelvis (ICD-7 : 180.1)		13	10.0	1.3	0.7–2.2	21	14.8	1.4	0.9–2.2	34	24.7	1.4	1.0–1.9

[a] This category (ICD 7 code 180) includes also parts unspecified (ICD 7 180.9). Obs, Observed; Exp, Expected

Table 3. Standardized incidence ratios (SIR) with 95 % confidence interval (CI) for renal cell cancer (ICD-7 : 180.0) among patients with diabetes mellitus, by completed years of follow-up and by year of birth

Determinant	Women				Men				Both sexes			
	Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI	Obs	Exp	SIR	95 % CI
Years of follow-up												
1–4	56	32.5	1.7	1.3–2.2	61	43.5	1.4	1.1–1.8	117	76.0	1.5	1.3–1.8
5–9	49	29.9	1.6	1.2–2.2	51	42.8	1.2	0.9–1.6	100	72.7	1.4	1.1–1.7
10–14	16	10.1	1.6	0.9–2.6	19	15.4	1.2	0.7–1.9	35	25.5	1.4	1.0–1.9
15–25	5	3.4	1.5	0.5–3.5	10	5.0	2.0	1.0–3.7	15	8.4	1.8	1.0–2.9
Year of birth												
< 1900	24	15.6	1.5	1.0–2.3	16	10.3	1.6	0.9–2.5	40	25.9	1.5	1.1–2.1
1900–19	86	49.5	1.7	1.4–2.2	86	69.0	1.3	1.0–1.5	172	118.5	1.5	1.2–1.7
1920–39	16	9.8	1.6	0.9–2.7	38	25.8	1.5	1.0–2.0	54	35.6	1.5	1.1–2.0
1940–	0	0.9	0.0	0.0–4.0	1	1.5	0.7	0.0–3.7	1	2.4	0.4	0.0–2.3

Obs, Observed; Exp, Expected

During the second up to the 25th year of follow-up, 267 incident renal cell cancers (ICD-7 : 180.0) occurred versus 182.4 expected, yielding an overall SIR of 1.5, with the relative risk being higher in women than in men (SIR = 1.7 vs 1.3). The SIR for renal pelvis cancer (ICD-7 : 180.1) was 1.4 for both sexes combined (Table 2). The risk of renal cell cancer stayed above expected throughout the duration of follow-up (Table 3).

We made several attempts to distinguish patients with Type I (insulin-dependent) diabetes mellitus from those with Type II (non-insulin-dependent) diabetes mellitus. Firstly, the relative risk of renal cell cancer was analysed by age at entry (start of follow-up). Although there was insufficient power to assess risks in younger patients, a clear excess risk was evident among women and men aged 40 years and older, but without any apparent trend (data not shown). Secondly, risk was analysed by year of birth, assuming that Type II diabetes predominated in the oldest birth cohort and Type I diabetes in the youngest. For both women and men born up to 1940, the excess risk of renal cell cancer was about 50 % in all birth cohorts. The numbers were too small, however, to evaluate risk among cohort members born after 1940 (Table 3).

Patients who had a diabetes diagnosis accompanied by acidosis complications, an indicator of Type I diabetes, had a relative risk of 1.2 (95 % CI = 0.7–2.0), whereas those with no history of acidosis had a risk of 1.5 (95 % CI = 1.3–1.7). The risk was similar for patients with a diabetes diagnosis indicating renal complications (ICD-7 codes 260.30; 592.02; 603.09; 792.99; ICD-8 codes 250.04; 593.28; 582.00; 792.99) (SIR = 1.3; 95 % CI = 0.5–2.8) and those with no record of renal complications (SIR = 1.5; 95 % CI = 1.3–1.7). Two of the renal cell cancer patients had a diagnosis of uraemia but none had a renal transplantation prior to renal cell cancer diagnosis. We further stratified the cohort patients by presence or absence of a history of inpatient diagnosis of obesity or hypertension. The relative risk for renal cell cancer (ICD-7 : 180.0) was 1.4 (95 % CI = 1.2–1.6) for those with no record of either obesity or hypertension and 1.9 (95 % CI = 1.4–2.4) for those with a history of either condition. Diabetes patients with obesity had a relative risk of 3.2 (95 % CI = 1.9–5.1) and patients who never had a discharge diagnosis of obesity had a relative risk of 1.4 (95 % CI = 1.2–1.6). Likewise, the risk for patients with and without hypertension were 1.7 (95 % CI = 1.2–2.3) and 1.4 (95 % CI = 1.2–1.6), respectively. In an additional multiplicative Poisson regression model including diagnose codes for obesity and hypertension, however, the estimates did not substantially change (data not shown).

To evaluate the effect of changes in the World Health Organisation (WHO) criteria for diabetes mellitus, we stratified the analysis by cohort entry before 1980 compared with 1980 and later. The risks for renal cell cancer (ICD-7 180.0) were similar for the two time periods, with SIR 1.49 (95 % CI 1.29–1.72) for the period before 1980 and SIR 1.38 (95 % CI 1.07–1.75) for the period 1980 and later. We also stratified by cohort entry before 1969 compared with 1969 and later to evaluate the effect of the change in ICD revision. We found no statistically significant difference in SIRs between the periods, with SIR 1.92 (95 % CI 1.31–2.73) for the period before 1969 and SIR 1.42 (95 % CI 1.24–1.61) for the period 1969 and later. Most of the data were from after 1969; 31 compared with 236 observed renal cell cancer incidences among diabetes patients included before and after 1969, respectively.

Since the observed excess of kidney cancer could be ascribed – at least theoretically – to detection bias resulting from the increased medical surveillance, i. e. detection of cancers that otherwise would have gone undiagnosed, we analysed mortality from kidney cancer (ICD-7 : 180). We also estimated lung cancer risk to indirectly evaluate whether smoking might be more common among cohort members than in the general population. We observed a statistically significant excess risk for mortality from kidney cancer (SMR = 1.9; 95 % CI = 1.7–2.2, women; SMR 1.7 95 % CI = 1.4–1.9, men). Mortality from lung cancer was close to the expected, as was incidence (SMR = 1.1; SIR = 1.2).

Discussion

Past studies have suggested that smoking, obesity, and possibly hypertension are risk factors for renal cell cancer, whereas the role of diabetes in the aetiology of this cancer remains unclear. A few studies attempted to investigate renal cell cancer risk among diabetic patients but low statistical power prohibited any conclusive results. Although some investigators observed no increased risk [6–8], others reported non-statistically significant increased risks [9, 10], or an association confined to women [12–17]. Our cohort study, the largest so far, sheds new light on the potential excess risks of renal cell cancer among diabetic patients. Both women and men with a history of diabetes had about 50 % excess risk regardless of birth year, duration of follow-up, or the presence of other risk factors for renal cell cancer, i. e. obesity and hypertension. Our finding supports the recent large-scale, multi-centre case-control study of renal cell cancer, which observed a 40 % increased risk for a self-reported history of diabetes [11].

The strengths of our study include the population-based cohort design, complete long-term follow-up of incidence and mortality [28], both exposure and outcome information verified by physicians and a large sample size. We had limited potential to study risk by age at diabetes onset since in-patient care could have taken place before the start of in-patient registration and patients may not have been admitted to hospital until after complications had arisen, perhaps many years after onset of the disease. As most of our patients were born, however, before 1920 and since relatively few patients with Type I diabetes in these birth cohorts ever reached the age of 60, our results pertain mainly to Type II diabetes.

During the study period criteria for diagnosing diabetes have changed and a change in ICD-revision has occurred which could possibly have an effect on the risk ratios. In our data we found no material difference in renal cell cancer risk with WHO or ICD changes between time periods for change, respectively.

It is unclear to what extent the cohort recruited from in-patient care is representative of all patients with diabetes mellitus. Patients with a long-standing disease or complications or both are more likely to be treated as in-patients, although in our cohort, increased risks were also seen among diabetic patients with no report of complications. Increased surveillance among patients admitted to hospital might exaggerate the risk of cancer relative to the general population but it is unlikely to account for the excess mortality of kidney cancer among our cohort patients.

Selection bias could also be introduced if there is a regional variation in kidney cancer incidence due to differences in exposures. The incidence of kidney cancer in the parts of Sweden that were not completely covered by hospital discharge registration was, however, close to that in the total Swedish population; the age-adjusted incidence rates in these areas (weighted for number of years without coverage during 1964–1983) was 15.4 per 100 000 men a year (vs 15.8 per 100 000 men a year in the total Swedish population) and 9.5 per 100 000 women a year (vs 9.8 per 100 000 women a year in all of Sweden).

A more serious concern is the inability to control for possible confounding factors. Bias could be introduced if, for instance, arteriosclerotic disease (hypertension, cardiac insufficiency etc.) rather than diabetes was the main indication for hospital admission. Such disease can be caused by smoking and obesity or could require treatment with diuretics or other antihypertensives agents, which have been associated with the occurrence of renal cell cancer [31]. Furthermore, the use of diuretics and non-diuretic antihypertensives drugs have also been linked to Type II diabetes [32]. Considerable confounding by such factors, however, seems unlikely since no substantial change in the risk estimates were revealed in our stratified analyses and associations between hypertension or its treatment and renal cell cancer appear weak [5]. Moreover, mortality from lung cancer in the diabetes cohort was close to that expected, suggesting that confounding by smoking is unlikely in our data. On the other hand, adjustment for obesity is problematic. Obesity is a dominant risk factor for non-insulin-dependent diabetes and risk of diabetes increases continuously with increasing levels of BMI (body mass index) [33, 34]. Being even moderately overweight is strongly associated with both non-insulin-dependent diabetes [33] and renal cell cancer [14]. In our study, patients with a history of obesity had a higher relative risk of renal cell cancer than those without such a history, although the risks were statistically significantly increased in both. Nevertheless, the stringent criteria used for a clinical diagnosis of obesity and the likely under-reporting of this condition in the discharge records could entail residual confounding due to obesity, although the multi-centre case-control study adjusted for weight and cigarette smoking still found a significant 40 % excess risk for self-reported diabetes [11]. In the Poisson regression modelling including obesity and hypertension, however, we found no indication of confounding.

Renal cell cancer development in diabetic patients with obesity could be related to hormonal changes. Endogenous oestrogens influence the development of renal cell cancer [12, 35] and women with diabetes have been reported with high levels of endogenous oestrogens [13]. In our study as well as in past studies, the increased risk of renal cell cancer among obese diabetic patients was more striking among women than among men.

End-stage renal disease, an outcome of kidney damage in diabetic patients, possibly influences the development of renal cell cancer [36]. In many countries diabetes mellitus has become the most common cause of end-stage renal-failure. Although the incidence of nephropathy is higher in Type I diabetes, the incidence of end-stage renal disease from Type II diabetes is increasing [37]. Long-term dialysis associated with aquired cystic kidney disease and progressive development of cysts in a poorly or non functioning kidney is associated with an increased risk for renal cell cancer. This kidney disease is observed with a prevalence of 8 % in uraemic patients prior to start of dialysis and the proportion increases to exceed 90 % after 10 years of dialysis [38]. An increased risk is also seen in the native kidneys after renal transplantation [39–41]. None of the renal cell cancer patients in our study, however, had a prior renal transplantation. Whereas proliferation of proximal tubular epithelial cells has been identified as the major pathogenetic mechanism of cyst formation, hormones (e. g. oestrogens) and growth factors and their receptors may stimulate cell proliferation and promote carcinogenesis. This mechanism could also explain, in part, the onset of multiple renal adenomas and bilateral carcinomas that develop in acquired cystic kidney disease [42].

Raised growth factors and growth factor receptors are possibly involved in the development of renal cell cancer among diabetic patients [43]. The onset of clinical diabetes is preceded by years of chronic hyperinsulinaemia with an increased proportion of proinsulin and split products of proinsulin, molecules with some homology to the growth factor IGF-1 [25]. Early features of kidney involvement in diabetes include an increased glomerular filtration rate, microalbuminuria and renal hypertrophy [44]. The pathogenic significance of the hypertrophy of the kidney is still unclear, although it is suspected that it could have important implications in the ultimate expression of renal damage and carcinogenesis. Recent experimental evidence suggests that IGFs, transforming growth factors (TGFs) and epidermal growth factor (EGF) play a part in several renal diseases, e. g. diabetic renal hypertrophy, nephritis, chronic renal failure, and kidney tumours [43, 45, 46]. Further, EGF has been suggested as a mitogenic hormone which could be involved in the regulation of proliferation and differentiation of normal and neoplastic cells. An overexpression of epidermal growth factor receptor (EGF-R) mRNA, TGF-α, TGF-β and IGF-I has been documented in renal cell cancer [47, 48].

We conclude that diabetes mellitus is a risk factor for renal cell cancer. It remains unclear, however, whether diabetes is an independent causal factor or an intermediate step in the causal pathway between a predisposing condition (e. g. obesity) and renal cell cancer.

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